Gilenya®▼

0.5 mg hard capsules (fingolimod)

Physician's checklist:

Summary of recommendations

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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Considerations in Gilenya® (fingolimod)▼ patient selection

Gilenya is suitable for adult and pediatric patients (≥10 years old) for the treatment of highly active relapsing remitting MS (RRMS)*. While many patients may be suitable for treatment, the following section highlights patients in whom Gilenya is contraindicated or not recommended.

Considerations for treatment initiation

Gilenya causes transient heart rate reduction and may cause atrioventricular (AV) conduction delays following initiation of treatment. All patients should be monitored for a minimum of 6 hours on treatment initiation. Below is a brief overview of monitoring requirements. Refer to page 4 for more information.

Appropriate

Eligible adult and pediatric patients (≥10 years old) with highly active RRMS who have not responded to a full and adequate course of at least one disease modifying therapy or those with rapidly evolving, severe RRMS*.

Contraindications

Known immunodeficiency syndrome, patients with increased risk for opportunistic infections (including immunocompromised patients), severe active infections, active chronic infections, known active malignancies, severe liver impairment, severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs, patients with second-degree Mobitz type II AV block or third- degree AV block, or sick-sinus syndrome (if they do not wear a pacemaker), patients with a baseline QTc interval of ≥500 msec, patients who in the previous 6 months had myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure, or New York Heart Association class III/IV heart failure, pregnant women, women of child-bearing potential (WOCBP; including female adolescents) not using effective contraception, and patients with hypersensitivity to the active substance or to any of the excipients.

Not recommended

Consider only after performing risk/benefit analysis and consulting a cardiologist

Sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT-interval prolongation†, history of cardiac arrest, uncontrolled hypertension or severe sleep apnea.	▶ **At least overnight extended monitoring is recommended** ▶ **Consult cardiologist regarding appropriate first-dose monitoring**
Taking beta-blockers, heart-rate–lowering calcium channel blockers‡, or other substances that are known to lower the heart rate§.	▶ **Consult cardiologist regarding possibility of switching to non-heart-rate-lowering drugs** ▶ **If change in medication is not possible, extend monitoring to at least overnight**

*Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and pediatric patients aged 10 years and older: patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
†QTc >470 msec (adult females), >460 msec (pediatric females), or >450 msec (adult and pediatric males).
‡Includes verapamil or diltiazem.
§Includes Class Ia and Class III antiarrhythmics, ivabradine, digoxin, anticholinesteratic agents, or pilocarpine.

Recommended steps to managing patients on Gilenya

The checklist and schematic that follow are intended to assist in the management of patients on Gilenya. Key steps and considerations while starting, continuing, or discontinuing treatment are provided.

Prior to initiating treatment

- ☐ Treatment with Gilenya is not recommended in the following patients, unless anticipated benefits outweigh the potential risks:
  - Those with sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT-interval prolongation*, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnea
    - ☐ Seek advice from a cardiologist regarding the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended
  - Those receiving concurrent therapy with beta-blockers, heart-rate-lowering calcium channel blockers (e.g. verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic agents, or pilocarpine)
    - ☐ Seek advice from a cardiologist regarding a switch to non-heart-rate-lowering medicinal products prior to initiation of treatment
    - ☐ If heart-rate-lowering medication cannot be stopped, seek advice from a cardiologist regarding the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended
- ☐ For pediatric patients, assess Tanner staging, measure height and weight, and consider a complete vaccination schedule, as per standard of care
- ☐ Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines
- ☐ Conduct baseline electrocardiogram (ECG) and blood pressure (BP) measurement
- ☐ Avoid co-administration of anti-neoplastic, immunomodulatory or immunosuppressive therapies due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration
- ☐ Obtain recent (within 6 months) transaminase, and bilirubin levels
- ☐ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) that Gilenya is contraindicated in pregnant women and WOCBP not using effective contraception
- ☐ Gilenya is teratogenic. Confirm a negative pregnancy test result in WOCBP (including female adolescents) prior to starting treatment and repeat at suitable intervals during treatment
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) about the serious risks of Gilenya to the fetus
- ☐ Provide all patients, parents (or legal representatives) and caregivers with the Pregnancy-Specific Patient Reminder Card
- ☐ Counsel WOCBP (including female adolescents and their parents/caregivers) to avoid pregnancy and use effective contraception both during treatment and for 2 months after treatment discontinuation. Counselling should be facilitated by the Pregnancy-Specific Patient Reminder Card
- ☐ Delay initiation of treatment in patients with severe active infection until resolved
- ☐ Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post-marketing setting. Cancer screening (including a Pap test), and vaccination for HPV-related cancer is recommended for patients as per standard of care
- ☐ Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is recommended and treatment initiation should be delayed for 1 month to allow full effect of vaccination to occur
- ☐ Conduct an ophthalmologic evaluation in patients with history of uveitis or diabetes mellitus
- ☐ Conduct a dermatologic examination. The patient should be referred to a dermatologist in case suspicious lesions, potentially indicative of basal cell carcinoma, or other cutaneous neoplasms (including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma), are detected
- ☐ Provide patients, parents and caregivers with the Patients, Parent's and Caregiver's Guide

*QTc >470 msec (adult females), >460 msec (pediatric females), or >450 msec (adult and pediatric males).

Treatment initiation algorithm

All patients, including pediatric patients, need to be monitored for at least 6 hours during treatment initiation, as described in the algorithm below.

This procedure should also be followed in pediatric patients when the dosage is switched from 0.25 mg to 0.5 mg Gilenya once daily*

It should also be followed at re-initiation of treatment if Gilenya is discontinued for

- One day or longer within the first 2 weeks of treatment
- More than 7 days during weeks 3 and 4
- More than 2 weeks after the first month of treatment

In addition, for patients in whom Gilenya is not recommended (see page 2), advice should be sought from a cardiologist regarding appropriate monitoring;at least overnight monitoring is recommended for this group.

Monitor for a minimum of 6 hours

- ☐ Perform baseline ECG and BP measurement
- ☐ Monitor for a minimum of 6 hours for signs and symptoms of bradycardia, with hourly pulse and BP checks. If patient is symptomatic, continue monitoring until resolution
  - Continuous (real-time) ECG is recommended throughout the 6-hour period
- ☐ Perform ECG at 6 hours

☐ Did the patient require pharmacologic intervention at any time during the monitoring period?

▶ YES

Monitor overnight in a medical facility. The first-dose monitoring should be repeated after the second dose of Gilenya

▼ NO

☐ Did third-degree AV block occur at any time during the monitoring period?

▶ YES

Extend monitoring at least overnight, until the findings have resolved

▼ NO

At the end of the monitoring period, have any of the following criteria been met?

- ☐ HR <45 bpm, <55 bpm in pediatric patients aged ≥12 years old, or <60 bpm in pediatric patients aged 10 to <12 years of age
- ☐ ECG shows new-onset second-degree or higher AV block or QTc interval ≥500 msec

▶ YES

Extend monitoring at least overnight, until the findings have resolved

▼ NO

☐ At the end of the monitoring period, is the HR the lowest since the first dose was administered?

▶ YES

Extend monitoring by at least 2 hours and until the heart rate increases

▼ NO

First-dose monitoring is complete

BP=blood pressure; ECG=electrocardiogram; HR=heart rate; QTc=heart-rate–corrected QT interval.
*For pediatric patients (≥10 years old), the approved dosing for Gilenya is 0.25 mg once daily for patients weighing ≤40 kg, and 0.5 mg once daily for patients weighing >40 kg.

During treatment

- ☐ A full ophthalmologic assessment should be considered:
  - 3–4 months after starting treatment for the early detection of visual impairment due to drug-induced macular edema
  - During treatment in patients with diabetes mellitus or with a history ofuveitis
- ☐ Counsel patients to report signs and symptoms of infection immediately to their prescriber during, and for up to 2 months after, treatment
  - Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis and initiate appropriate treatment if diagnosed
    - Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on Gilenya treatment.
    - Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2–3 years of treatment, although an exact relationship with the duration of treatment is unknown
  - Be vigilant for clinical symptoms or MRI findings suggestive of progressive multifocal leukoencephalopathy (PML). If PML is suspected, treatment with Gilenya should be suspended until PML has been excluded
    - Cases of PML have occurred after approximately 2–3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown
  - Suspend treatment during serious infections
- ☐ Check full blood count periodically during treatment, at month 3 and at least yearly thereafter, and interrupt treatment if lymphocyte count is confirmed as $<0.2x10^9/L$*
- ☐ Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported
  - In the absence of clinicalsymptoms:
    - Check liver transaminases and serum bilirubin at months 1, 3, 6, 9, and 12 on therapy and periodically thereafter until 2 months after Gilenya discontinuation
    - If liver transaminases are greater than 3 but less than 5 times the upper limit of normal (ULN) without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present.
    - If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin,Gilenya should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), Gilenya may be restarted based on a careful benefit-risk assessment of the patient*
- ☐ While on treatment, women should not become pregnant. Discontinue treatment if a woman becomes pregnant. Gilenya should be stopped 2 months before planning a pregnancy, and the possible return of disease activity should be considered. An ultrasonography examination should be performed and medical advice about the harmful effects of Gilenya to the fetus should be provided.
- ☐ Advise WOCBP (including female adolescents and their parents/caregivers) that effective contraception must be used during treatment and for at least 2 months after treatment discontinuation. Pregnancy tests must be repeated at suitable intervals
- ☐ WOCBP (including female adolescents and their parents/legal representatives/caregivers) must be informed regularly about the serious risks of Gilenya to the fetus
- ☐ Ensure WOCBP (including female adolescents), their parents (or legal representatives), and caregivers receive regular counseling facilitated by the Pregnancy-Specific Patient Reminder Card
- ☐ To help determine the effects of Gilenya exposure in pregnant women with MS, physicians are encouraged to report pregnant patients who may have been exposed to Gilenya at any time during pregnancy (from 8 weeks prior to last menstrual period onward) to Novartis by dialing [insert local number] or visiting [insert URL https://psi.novartis.com or Novartis local website depending on local requirements], in order to allow monitoring of these patients through the Pregnancy Outcomes Intensive Monitoring Program (PRIM). Physicians may also enroll a pregnant MS patient under their care in the Gilenya Pregnancy Register by dialing [insert local number] or visiting [insert URL according to local requirements]
- ☐ Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended with skin examination every 6 to 12 months and referral to a dermatologist if suspicious lesions are detected
  - Caution patients against exposure to sunlight without protection
  - Ensure patients are not receiving concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy
- ☐ Gilenya has an immunosuppressive effect and can increase the risk of developing lymphomas (including mycosis fungoids), and other malignancies (particularly those of the skin), and serious opportunistic infections. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Closely monitor patients during treatment, especially those with concurrent conditions, or known factors, such as previous immunosuppressive therapy;

*Approved dose of 0.5 mg once daily (or 0.25 mg once daily in pediatric patients [≥10 years old] with a body weight of ≤40 kg) to be used when restarting treatment as other dosing regimens have not been approved.

and discontinue treatment if a risk is suspected

- ☐ Cases of seizure, including status epilepticus, have been reported. Vigilance for seizures, especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy, is recommended
- ☐ Monitor pediatric patients for signs and symptoms of depression and anxiety
- ☐ Reassess on an annual basis the benefit of Gilenya treatment versus risk in each patient, especially pediatric patients

After treatment discontinuation

- ☐ Repeat first-dose monitoring as for treatment initiation when treatment is interrupted for
  - One day or more during the first 2 weeks of treatment
  - More than 7 days during weeks 3 and 4 of treatment
  - More than 2 weeks after one month of treatment
- ☐ Counsel patients to report signs and symptoms of infection immediately to their prescriber for up to 2 months after discontinuation
  - ☐ Instruct patients to be vigilant for signs of encephalitis, meningitis or meningoencephalitis infection and PML
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) that effective contraception is needed for 2 months after discontinuation because of the serious risks of Gilenya to the fetus
- ☐ Advise women who stop treatment with Gilenya because they are planning a pregnancy that their disease activity may return
- ☐ Vigilance for the possibility of severe exacerbation of disease following discontinuation of treatment is recommended
  - In cases of severe exacerbation appropriate treatment should be initiated as required

Summary guidance specifically for pediatric patients

- ☐ Consider a complete vaccination schedule before starting Gilenya
- ☐ Counsel patients and their parents/caregivers on Gilenya's immunosuppressive effects
- ☐ Assess physical development (Tanner staging), and measure height and weight, as per standard ofcare
- ☐ Perform cardiovascular monitoring
- ☐ Perform first-dose monitoring on treatment initiation due to the risk of bradyarrhythmia
- ☐ Repeat first-dose monitoring in pediatric patients when the dosage is switched from 0.25 mg to 0.5 mg Gilenya once daily*
- ☐ Emphasize the importance of treatment compliance to patients, especially with regard to treatment interruption and the need to repeat first-dose monitoring
- ☐ Monitor the patient for signs and symptoms of depression and anxiety
- ☐ Provide guidance on seizure monitoring

*For pediatric patients (≥10 years old), the approved dosing for Gilenya is 0.25 mg once daily for patients weighing ≤40 kg, and 0.5 mg once daily for patients weighing >40 kg.

For more detailed guidance on GILENYA please refer to the Summary of Product Characteristics (SmPC) available at https://www.ema.europa.eu/en/medicines/human/EPAR/gilenya

Suspected Adverse Drug Reactions (side effects) and medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal and sent by post or email to;

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann. SGN 3000.

E: postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events associated with the use of **Gilenya** to Novartis Pharma Services Inc., Representative Office, Malta, by phone on +356 21222872, online on www.report.novartis.com or by e-mail at drug_safety.malta@novartis.com.

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